REMARKS

Claims 1, 3, 4, 8-10, 13-15, 28, 29, and 33-44 are pending in the application. Claim 43 has been amended. This amendment merely clarifies the form and does not change the substance of the claim. Applicants respectfully assert that no new matter has been added and request reconsideration of the claims currently pending in the application.

Applicants wish to thank the Examiner for favorable consideration and allowance of claims 28, 29, and 33, as well as indicating the allowability of claims 42-43.

1. Double patenting rejection

On page 3 of the Office Action, claims 1, 3, 4, 8-10, 13-15, and 34-40 were provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1, 2, 4-11, 14, 15, and 21-29 of copending Application No. 09/014,087. The Examiner contends that the present claims are obvious over the copending claims because the same embodiment is set forth herein such that the claims sets read on each other and is clearly obvious in view of each other. The Examiner notes that this is a provisional obviousness-type double patenting rejection.

While Applicants continue to believe that the claims now pending in the present application are not obvious over claims of copending Application No. 09/014,087, Applicants will consider submitting a terminal disclaimer once claims of one or both applications are found to be allowable and the double-patenting rejection is no longer provisional. In the meantime, Applicants respectfully request that the Examiner hold in abeyance this requirement. Reconsideration is respectfully requested.

II. Rejection under 35 U.S.C. § 112

On page 2 of the Office Action, claim 43 is rejected under 35 U.S.C. §112 second paragraph for being indefinite.

The Examiner rejected claim 43 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. The Examiner asserts that claim 43 appears to limit the claim to a crosslinking agent only because the word "comprises" is used followed by "a crosslinking agent," and for this reason, it is unclear whether the crosslinking agent is an additional element of the claim or the entire device. In addition, the Examiner contends that claim 43 now lacks a period, and suggests that Applicants change "comprising" to --further comprising-- and to add a period in order to overcome this rejection.

The Applicants respectfully traverse this rejection, but have amended the application according to the Examiner's suggestion to overcome the objections. Claim 43 has been amended. This amendment merely clarifies the form and does not change the substance of the claim.

Applicants respectfully assert that all claims comply with 35 U.S.C. §112 and request the rejection be withdrawn.

III. Rejection under 35 U.S.C. §102

On page 4 of the Office Action, claims 1, 3, 4, 8, and 9 are rejected under 35 U.S.C. §102 (b) as being anticipated by Cahalan, et al. (U.S. Patent Number 5,308,641). The Examiner notes that the substrate as claimed in the present invention is the polyalkylimine coated tissue of Cahalan and the growth factors are coated via

glutaraldehyde (a crosslinking agent) to it; see especially column 4, lines 20-43 and column 6, lines 8-28 and the abstract, column 4, lines 20-43, and column 6, lines 8-28. The Examiner further notes that "fixed" and "crosslinked" are synonymous in the tissue graft implant art. Thus, the Examiner contends that Cahalan discloses that one purpose of the surface treatment is to "promote the attachment and growth of normal cell layer" see column 1, lines 33-43, and for this reason, it stimulates the "association of viable cells with the substrate" as claimed.

Applicants respectfully traverse the rejections.

The Cahalan, et al. patent teaches the use of a spacer, which presents a stable platform for the attachment of the biomolecule. See col. 2, lines 63-66. All the objects of the invention recite the use of a spacer. Col. 2, lines 58-68. The spacer is strongly attached to the material surface, is present between the substrate and the biomolecule, and sometimes, a second spacer is used. See col. 2, lines 58-68, col. 4, lines 62-66, and col. 5, lines 44-55. The polyalkylimine and crosslinking agent together form the spacer used for improving the biocompatability of the substrate to enable the attachment of a biologically active compound to the substrate through the spacer. See col. 4, lines 14-19. Cahalan, et al. further stress that the spacer is there to present a stable platform to prevent the biomolecule from being buried in the spacer layer. Col. 2, lines 63-66. Cahalan, et al. also note that the light crosslinking of polyalkylimine to the substrate and the light crosslinking in the interface between the polyalkylimine and the biomolecule to attach the biomolecule to the polyalkylimine is necessary to prevent the biomolecule from being buried in the spacer and losing bioactivity (col. 2, lines 63-66 and col. 3, lines

2-20). Thus, there is no teaching of direct crosslinking of the growth factor to the substrate due to the presence of this spacer.

While Applicants agree that that "fixed" and "crosslinked" can be synonymous in the tissue graft implant art, and that Cahalan, et al. possibly disclose that one purpose of the surface treatment is to "promote the attachment and growth of normal cell layer" in column 1, lines 33-43, the surface treatment is what Cahalan, et al. is teaching, and the spacer is their center piece, to prevent the biomolecule from being buried in the spacer layer.

On the other hand, the subject matter of claim 1 of the present invention is related to a biomedical device comprising the association with or direct crosslinking of a growth factor to a substrate. No spacer is present.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. Applicants respectfully submit that Cahalan, et al. do not teach every element of claim 1, and therefore fails to anticipate claim 1.

Dependent claims 3, 4, 8 and 9, which are dependent from independent claim 1, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Cahalan, et al. While Applicants do not acquiesce with the particular rejections to these dependent

claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features, which further distinguish these claims from the cited references. Therefore, dependent claims 3, 4, 8 and 9 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejections of claims 1, 3, 4, 8, and 9 under 35 U.S.C. §102 (b) as being anticipated by Cahalan, et al.

IV. Rejection under 35 U.S.C. §103

A. On page 4 of the Office Action, claims 10 and 15 are rejected under 35 U.S.C. §103(a) as being unpatentable over Cahalan, et al. in view of Goldstein (U.S. Patent No. 5,613,982).

The Examiner notes that Cahalan discloses medical devices/implants where the crosslinking agent glutaraldehyde attaches the growth factor biomolecule to the substrate-spacer and Cahalan's solid surface can be made of human or animal tissues, but Cahalan lacks the types of tissues claimed.

However, the Examiner notes that Goldstein teaches that it was known to make similar medical devices/implants out of heart valves, pericardial tissue and the like; see the whole document, especially column 3, lines 14-24.

Therefore, it is the Examiner's position that it would have been obvious to use heart valve or pericardial tissue for Cahalan's solid surface in order to reduce the risk of disease transmission and cost over using human animal tissue. Furthermore, the

Examiner contends that it would have been obvious to use these tissues for the same reasons that Goldstein desires the same.

Applicants respectfully traverse the rejections.

As discussed above, Cahalan, et al. teaches the use of a spacer. The spacer is present between the substrate and the biomolecule. See col. 2, lines 58-68. Thus, Cahalan, et al. not only fails to teach association with or direct crosslinking of a growth factor to a substrate without a spacer material, it teaches away from such association or direct crosslinking. The solid surface of Cahalan, et al. is not the substrate, but the spacer, as Cahalan, et al. stress that the spacer is there to present a stable platform to prevent the biomolecule from being buried in the spacer layer. Col. 2, lines 63-66. One can certainly give any name to the combination of spacer/substrate, but that still does not defeat the purpose that the spacer is present on the substrate and thus will prevent any direct attachment of other materials onto the substrate, especially in view of Cahalan, et al.'s teaching that the spacer presents a stable platform for the attachment of biomolecules and thereby prevents the attached biomolecule from being buried in the spacer layer. Col. 2, line 63-66.

At the same time, Goldstein teaches a method of preparing a xenogeneic tissue matrix by removing native cells and other antigens from the tissue matrix. See col. 2, lines 44-63. In addition, even though Goldstein teaches the generating of bioprosthetic xenografts suitable for human implantation, and mentioned heart valve tissues of porcine or bovine origin (col.3, lines 14-24), it mainly teaches that various enzymatic and chemical treatments to remove viable native cells from implant tissues and organs may be used. See col. 5, lines 12-19. Such removal treatment does not relate to the

association of cells or growth factors. Therefore, Goldstein also fails to teach association with or direct crosslinking of a growth factor to a substrate to stimulate the association of viable cells with the substrate.

Claim 1 of the present invention teaches association with or direct crosslinking of a growth factor to a substrate without a spacer material. This deficiency is found in both Cahalan, et al. and especially Goldstein, which does not teach association with or direct crosslinking of a growth factor to a substrate to stimulate the association of viable cells with the substrate.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Since Cahalan, et al. teach away from association with or direct crosslinking of a biologically active compound to a substrate, and Goldstein teaches removal rather than association, the deficiency in Cahalan is therefore not supplied by Goldstein. Applicants respectfully traverse the rejection since the prior art fails to disclose all the claim limitations and there would be no motivation to combine the references as proposed by the Examiner.

Claims 10 and 15 are dependent from claim 1. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. These dependent claims include all of the limitations of claim 1 and any intervening

claims. Claims 10 and 15 are therefore allowable over Cahalan, et al., in view of Goldstein.

Applicants respectfully request withdrawal of the rejection of claims 10 and 15 under 35 U.S.C. §103(a) as being anticipated by Cahalan, et al. in view of Goldstein.

B. On page 5 of the Office Action, claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Cahalan, et al. in view of Bayne, et al. (EP 0476983).

With regard to claim 13, the Examiner admits that Cahalan fails to disclose the VEGF claimed even though it discloses many other growth factors therewith. However, the Examiner asserts that Bayne, et al. teach that it was known to use VEGF as the growth factor in a similar fashion within the same art; see the whole document.

Therefore, it is the Examiner's position that it would have been obvious to an ordinary artisan to use VEGF as the growth factor of Cahalan so that the implant could be successfully implanted in vascular regions of the body.

Applicants respectfully traverse the rejection.

The deficiency of Cahalan, et al., as discussed above, is also applicable here. Bayne, et al. teach a vascular endothelial cell growth factor isolated and purified from glioma cell conditioned medium. See page 3, lines 46-55. The main focus of Bayne, et al. is on the isolation and characterization of VEGF II mammalian glioma cells. See examples in Bayne, et al. In addition, Bayne, et al. disclose growing cells in the presence of VEGF in a culture medium. Page 8, lines 8-17. After sufficient cells are grown, the cells are then plated on the inside surface of a vessel. Page 8, lines 17-19. Thus, Bayne, et al. also fail to teach association with or direct crosslinking of a growth

factor to a substrate. See page 8, lines 20-23. The deficiency in Cahalan, et al. is thus not supplied by Bayne, et al. and there is no motivation in Cahalan, et al. to combine with Bayne, et al. to arrive at the present invention.

Claim 13 is dependent from claim 1. While Applicants do not acquiesce with the particular rejections to it, it is believed that the rejection is moot in view of the remarks made in connection with independent 1. Dependent claim 13 includes all of the limitations of the base claim and any intervening claims, and recite additional features, which further distinguish it from the cited references. Therefore, dependent claim 13 is in condition for allowance

Applicants respectfully request withdrawal of the rejection of claim 13 under 35 U.S.C. §103(a) as being anticipated by Cahalan, et al. in view of Bayne, et al.

C. On page 5 of the Office Action, claims 41 and 44 are rejected under 35 U.S.C. §102(a) as being unpatentable over Sharp, et al. (WO 98/00695), or alternatively, under 35 U.S.C. §103(a) by Sharp, et al. alone.

Regarding claim 41, the Examiner notes that the body of the claim does not require the preamble for completeness such that Tat protein bound to a test substrate reads on the claim language. The Examiner further notes that this Tat protein-to-substrate binding would inherently be done with an enzyme-substrate association because enzymes are proteins as are Tat proteins and would have inherently have to be bound in the same way to a substrate.

Alternatively, the Examiner notes that one could take the position that the binding of the Tat protein to the substrate is not an enzyme-substrate association because it is

not explicitly stated as such. However, the Examiner posits that it would have been a matter of obvious design choice to bind the Tat protein to the substrate with an enzyme-substrate association because Applicants have not disclosed that it would provide some advantage, is used for a particular purpose, or solves a stated problem. Further, the Examiner contends that one of ordinary skill in the art would have expected Applicants' invention to perform equally well, and therefore would have been an obvious matter of design choice to modify Sharp to obtain the invention as specified in the claims.

With regard to claim 44, the Examiner notes that the enzyme-substrate association is the type of association which is present in the Sharp device.

Applicants respectively traverse the rejection.

Sharp, et al. disclose the identification, purification and isolation of proteins, Tat-Stimulatory Factor proteins. See page 3, lines 19-22. Further, they disclose the discovery and identification of kinases that bind the Tat-Stimulatory Factor proteins. See page 3, lines 23-25. A solution suspected of containing the kinases is applied to the Tat-Stimulatory Factor-bound substrate and the kinases are isolated and identified. See page 17, line 29 to page 18, line 4. There is no disclosure or teaching in Sharp that the Tat-Stimulatory Factor protein is associated with the substrate, effective to stimulate the association of viable cells with the substrate as the substrate-bound Tat-Stimulatory Factor protein is mainly used to bind the kinases, the natural binding partners for Tat-Stimulatory Factor proteins so that the kinases may be isolated, and the Tat-Stimulatory Factor proteins are used as the substrate in such isolation. See page 17, line 29 to page 18, line 4. This isolation process is similar to isolation by successive fractionation not involving any substrate. See page 18, lines 1-4. Thus, Sharp, et al. are not

concerned with using the Tat protein to stimulate the association of viable cells with substrates, the subject matter of claim 41.

Maybe the Tat protein in Sharp, et al. will also stimulate the association of cells if it is not present in a solution containing kinases. However, since it is in such a state and is bound to the kinases, it does not stimulate association of cells on the substrate.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102(a).

Therefore, since Sharp, et al. do not teach every element of claim 41, Sharp et al. do not anticipate claim 41.

Claim 44 is dependent on claim 41 and is also rejected over Sharp, et al. under 35 U.S.C. §102(a). Applicants submit that in view of the remarks made in connection with the independent claim, this rejection of claim 44 is moot and claim 44 is also in condition for allowance. Reconsideration is respectfully requested.

Alternatively, if, as the Examiner contends, that even though there is no explicit disclosure that this Tat protein-to-substrate binding is done with an enzyme-substrate association, but since enzymes are proteins as are Tat proteins, they would inherently have to be bound in the same way to a substrate, then Applicants submit that the Tat

protein will not be free to bind with kinases, its natural binding partner, if this is true. The Tat protein will inherently have to bind to a substrate in the same manner each time if the purpose of such binding is the same each time. Since the purpose of the substrate-bound Tat protein in Sharp, et al. is to bind and isolate kinases out of a solution medium, which is different from stimulating association of viable cells on the substrate, the subject matter of claim 41, it does not necessarily follow that just because Tat protein is mentioned in Sharp, et al., the association of Tat protein to the substrate in Sharp, et al. is inherently the same as the association of Tat protein to the substrate in claim 41. As claim 41 represents a completely different invention from the purpose of Sharp, et al., the invention of claim 41 is not a matter of obvious design choice of modifying Sharp, et al., since there is no teaching or motivation in Sharp concerning the association of Tat protein growth factors for stimulating the association of viable cells with the substrate, It may be the Tat protein in Sharp, et al. will also stimulate the association of cells if it is not present in a solution containing kinases. However, since it is present in such a state and is bound to the kinases, it does not stimulate association of cells on the substrate. Rather, the Tat protein associates with the kinases leading to their isolation. Applicants respectfully submit that the three criteria to establish a *prima facie* case of obviousness are not met since the reference does not teach or suggest all the claim limitations. MPEP § 2142. The prior art fails to disclose all the claim limitations and there would be no motivation to combine the references as proposed by the Examiner. Therefore, the rejection of claim 41 under 35 U.S.C. § 103(a) as being unpatentable over Sharp, et al. is traversed.

Dependent claim 44, which is dependent from independent claim 41, was also rejected under 35 U.S.C. §103(a) as being unpatentable over Sharp, et al. While Applicants do not acquiesce with the particular rejection to this claim, it is believed that the rejection is moot in view of the remarks made in connection with independent claim 41 since claim 44 includes all of the limitations of claim 41, and recites additional features which further distinguish these claims from the cited references. Therefore, dependent claim 44 is also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 41 and 44 under 35 U.S.C. §102(a) as being anticipated by Sharp, et al., or alternatively, under 35 U.S.C. §103(a) by Sharp, et al. alone.

V. Allowable Subject Matter

The Examiner agrees that claims 28, 29, and 33 are allowed over the prior art of record.

The Examiner notes that claim 42 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and claim 43 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office Action and to include all of the limitations of the base claim and any intervening claims.

Applicants have amended claim 43 as proposed by the Examiner. As this amendment does not change the substance of claim 43, the scope of the claim remains the same.

Applicants submit that in view of the remarks made above in connection with claim 41 that claims 42 and 43 are also in condition for allowance. Reconsideration is respectfully requested.

VI. Response to Arguments

A. With regard to the traversal of the double patenting rejection, the Examiner notes that no reasons were given for the distinctness of the two claims sets; only the Applicants' opinion was given. Thus, the Examiner notes that no further comment is deemed necessary.

Applicants have addressed this rejection above and respectfully request reconsideration in view of the remarks made.

B. The Examiner, in response to the argument traversing the Cahalan rejection that Cahalan lacks direct crosslinking of the growth factor to the substrate without a spacer molecule, asserts that the claims do not preclude a spacer molecule and that the claims are read on by Cahalan, and thus this argument is not commensurate with the scope of the claims.

Applicants respectfully traverse this contention.

Claim 1 recites "to link the crosslinking agent directly with the polypeptide growth factor and the substrate" (emphasis added). Since "direct" does not mean "having a spacer interposed in between", there is no room for a spacer in "direct" linking. Reconsideration is respectively requested.

C. The Examiner, in response to Applicants' argument that the crosslinking agent in Cahalan is used to attach polyalkylimine to the surface and not to the biomolecules, asserts that the opposite is true, because the crosslinking agent (an aldehyde) crosslinks the surface and provides aldehyde functionalities to the surface to bind biomolecules; see column 2, line 66 to column 3, line 3.

Applicants respectfully traverse this contention.

Applicants submit that this contention is moot in view of the discussion above that the Cahalan, et al. patent teach the use of a spacer which presents a stable platform for the attachment of the biomolecule (see col. 2, lines 63-66); that the spacer is present between the substrate and the biomolecule (see col. 2, lines 58-68); that the polyalkylimine and crosslinking agent together form the spacer used for improving the biocompatability of the substrate to enable the attachment of a biologically active compound to the substrate through the spacer (see col. 4, lines 14-19); and that Cahalan, et al. note that the light crosslinking of polyalkylimine to the substrate and the light crosslinking in the interface between polyalkylimine and the biomolecule to attach the biomolecule to the polyalkylimine is necessary to prevent the biomolecule from being buried in the spacer and losing bioactivity (col. 2, lines 63-66 and col. 3, lines 2-20). Thus, there is no direct crosslinking of the growth factor to the substrate due to the presence of this spacer in Cahalan, et al. Reconsideration is respectfully requested.

D. In response to the traversal of Cahalan that association of the growth factors is not made by antibody-antigen, specific binding protein, or enzyme associations, the Examiner notes that the association is made by the other association claimed; i.e. the

crosslinking agent association. The Examiner notes that Applicants also suggest that Cahalan, et al. do not teach stimulation of the association of viable cells to the substrate as claimed when Cahalan discloses that one purpose of the surface treatment is to "promote the attachment and growth of normal cell layer," see column 1, lines 33-43. For this reason, the Examiner contends that the claim language is considered to be fully met in this regard.

Applicants respectfully traverse this contention and cite the discussion above concerning Cahalan, et al. in response. The substrate of Cahalan, et al. has a spacer interposing between the substrate and the biomolecule, in the case when a crosslinking agent is used, and thus the biomolecule is not directly linked to the substrate, unlike that of the present invention. Reconsideration is respectfully requested

E. In response to the traversal of the Sharp rejection that there is no evidence that the Tat protein of Sharp stimulates the attachment of viable cells to the substrate, the Examiner asserts that claim 41 does not require any particular amount of growth factor. In fact, the Examiner asserts that it appears that only one molecule of growth factor is required because no effective amount has been claimed. Furthermore, the Examiner notes that the Tat protein of Sharp inherently stimulates attachment of viable cells to the substrate, because it is the same molecule as Applicants claim. Thus, the Examiner contends, one cannot get a patent on the discovery of a new property in an otherwise old device.

Applicants respectfully traverse this contention.

As discussed above, the present invention is distinguished from that in Sharp, et al., as Sharp, et al. are concerned with the discovery and identification of kinases that bind the Tat-Stimulatory Factor proteins. See page 3, lines 23-25. A solution suspected of containing the kinases is applied to the Tat-Stimulatory Factor-bound substrate and the kinases are isolated and identified. See page 17, line 29 to page 18, line 4. There is no disclosure or teaching in Sharp that the Tat-Stimulatory Factor protein is associated with the substrate, effective to stimulate the association of viable cells with the substrate. In fact, no cells are being associated with the substrate. The substrate-bound Tat-Stimulatory Factor proteins are mainly used to bind the kinases, the natural binding partners for Tat-Stimulatory Factor proteins so that the kinases may be isolated, and the Tat-Stimulatory Factor proteins are used as the substrate in such isolation. See page 17, line 29 to page 18, line 4. Thus, Sharp, et al. disclose using the Tat proteins to bind and isolate the kinases, while the present invention relates to associating the Tat protein with a substrate to stimulate associations of cells on the substrate. It may be the Tat protein in Sharp, et al. will also stimulate the association of cells if it is not present in a solution containing kinases. However, since it is in such a state and is bound to the kinases, it does not stimulate association of cells on the substrate. Reconsideration is respectfully requested.

VII. Conclusion

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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